medicine or a vaccine for the therapy or prevention of prion diseases, or the vaccination against prion diseases.--

REMARKS

The last Official Action has been carefully considered. Claims 77 through 117 are presented herewith. The Examiner will note that many of the new claims are identical to the previously submitted claims but for simplicity sake and to facilitate the Examiner's work, all the claims have been rewritten and renumbered. The claims that the Examiner indicated as allowable, i.e., corresponding to the deposit, namely previous claims 52, 53 and 54 are, of course, contained in the rewritten set and are thus now allowable. The rewritten claims have also been corrected as to improper multiple dependency as objected by the Examiner in the last paragraph on page 3 of the Action.

In view thereof, it is believed that the withdrawn claims 55 through 56, 69 through 71 and 73 through 76 which have been rewritten should also be considered by the Examiner and should be allowable for the same reasons as the other claims.

Reconsideration of the rejection of the claims under 35 U.S.C. 102(e) as being anticipated by Pruisiner, et al. (U.S. Pat. No. 5,846,533) as evidenced by Billeter, et al. (PNAS 1997) is respectfully requested. Dr. Moser, one of the co-inventors, who participated in the telephone conference of February 11, 2003 and who is an internationally recognized authority in the field has commented in detail on the distinction between Pruisiner and the

present invention as recited in the claims. His comments and arguments which persuasively rebut the Examiner's position are recited herein in full.

At present it is thought that the infectious agent for prion diseases is associated with a disease specific prion protein PrP^{Sc} being an abnormal isoform of the host protein PRP^{C}. Both isoforms have the same apparent molecular weight of 32-35kD. One important difference between the two forms is that after proteinase K treatment PRP^{C} is fully destroyed while PrP^{Sc} only looses its N-Terminus thereby being shortened to a 27-30kD fragment. In the prion terminology PrP27-30 is therefore denominating the 27-30kD fragment of PrP^{Sc} left after protease treatment.

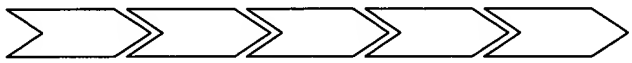
To date no chemical differences between the two PrP isoforms, PRP^{C} and PrP^{Sc}, have been found. It is therefore assumed, that the only difference lies in their 3-D structure. The exact structure has not been determined for either of the two isoforms (note: the NMR structure of recombinant PrP was resolved in 1997 and to date serves as a model for PRP^{C}) but it has been clearly shown by IR-spectroscopy that PrP^{Sc} has a higher beta-sheet content than PRP^{C}, while conversely PRP^{C} has a higher alpha-helix content.

The present theories for prion diseases postulate that PrP^{Sc} is able to convert the normal PRP^{C} protein of an infected host to PrP^{Sc} thereby causing progression of the infection.

PrP^{Sc} has a tendency to form aggregates, as many proteins with high content of beta-sheet structures do. In vivo, PrP^{Sc} aggregation leads to the formation of plaque-deposits in the brain of diseased organisms. In vitro, the process of PrP^{Sc} purification by limited proteolysis with proteinase K even increases the tendency of the molecules to aggregate and produces so-called PrP27-30 rods which are so large in size that they can be visualized by electron microscopy (McKinley et al., 1991).

In summary, PRP^{C} is a protease-sensitive molecule with high alpha-helix structure content, while PrP^{Sc} has a 27-30kD protease resistant core and a high content of beta-sheet structures. PrP^{Sc} has a tendency to form aggregates in vivo and, after in vitro treatment with proteinase K even forms extensive rods consisting of PrP27-30.

To immunize mice with prion protein purified fractions of mammalian prion protein (eg. PrP^{Sc} purified by proteolysis, resulting in PrP27-30 rods) can be used. Pruisiner et al. used PrP27-30 rods for immunization (see example 2). Molecules polymerizing to form rods are expected to have many epitopes which would not efficiently be available for immunogenic reactions as these epitopes are not presented at the rod surface:

e.g.: 

The drawing above illustrates that those surfaces of the molecules involved in polymerization / aggregation are not extensively available on the surface of the rod.

As aggregation is a property of the PrP^{Sc}-conformation but not of the PRP^{C}-conformation, it is conceivable that epitopes specific for the PrP^{Sc}-conformation would be localized at the contact-sites of the PrP^{Sc} molecules rather than at the rod surface.

Further masking of epitopes in PrP27-30 rods might occur by sulphated glycans which are part of PrP^{Sc} aggregates and are thought to be an essential cofactor for the formation of such aggregates (Caughy and Raymond, 1993).

Korth et al. were the first to chose an alternative immunization strategy aiming at presenting to the immune system the maximum possible number of epitopes of both PRP^{C} and PrP^{Sc} by immunizing with a mixture of oxidized and reduced recombinant PrP (rPrP). It has been shown that oxidized rPrP has a predominantly alpha-helical structure like PRP^{C} whereas reduced rPrP has a high beta-sheet content like PrP^{Sc} (Mehlhorn et al. 1996). Although reduced rPrP is soluble it still has a tendency to aggregate, particularly at pH values above 7. In conclusion, a mixture of reduced and oxidized rPrP contains a mixture of structural elements characteristic for PRP^{C}, monomeric PrP^{Sc} and multimeric PrP^{Sc}. This "structure cocktail" serves to challenge the immune system of the immunized mice with the maximum variety of PrP structures and was therefore expected to produce the maximum variety of possible antibodies against the various PrP isoforms.

It is the applicants firm belief that only from such maximum variety of PrP structures the antibodies of the present application, including AB 15B3 with its new properties, could be obtained. If applicant's approach had not yielded AB 15B3 this would have been a direct indication that PrP^{Sc} does not possess conformation specific epitopes or that PrP^{Sc} conformation specific epitopes could not be mimicked by rPrP. Conversely, however, the fact that AB 15B3 was produced proves that the applicant's method served to present the mouse immune system with PrP^{Sc} specific epitopes.

It is believed that the above arguments which are applicable to all the claims now in the case convincingly and persuasively demonstrate the patentability of the claims over Pruisiner. The Examiner is respectfully requested to withdraw the 102(e) rejection.

As to Billeter, the Examiner, in the office action, concedes that normally, a 102 rejection should be based on a single reference only. The Examiner cites then MPEP 2131.01 which lists certain exceptions to the general rule and in particular refers to the rejection over multiple references where the extra reference is cited to "show that a characteristic not disclosed in the primary reference is inherent." While applicants have no quarrel with the Examiner's position in this respect and are aware of the propriety to cite two references under Section 102 under the indicated circumstances, it is believed that the "inherency" on which the Examiner relies is no longer pertinent or relevant in view of the above remarks.

Moreover, the Examiner is requested to withdraw the publication because even if the inherency issue is properly relied upon by the Examiner, the secondary or extra reference was published after the priority date of the present application. Surely, the Examiner is not entitled to rely for any purposes whatsoever on a reference which has no standing under the law because of its late date. In this context, the Examiner is respectfully directed to the faxed communication sent to her on January 10, 2003 with attachment. That communication referred the Examiner to the decision of the Federal Circuit in *Ciba Geigy Corp. v. Alza Corp.* 37 U.S.P.Q. 2D and in particular to a check-marked sentence reading: "Thus, although references cannot be combined for purposes of anticipation, additional references may be used to interpret the allegedly anticipating reference and shed light on what it would have meant to those skilled in the art at the time of invention." (Emphasis supplied). At the time of invention, the extra reference was not available and accordingly is not available to the Examiner for any purpose whatsoever.

In the Office Action and during the telephone conference, the Examiner stated that claims directed to the deposit are clearly allowable. These claims should thus now be allowed as should all the other claims in view of the arguments submitted herewith.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance, and allowance of the application is respectfully requested.

If any fee is required with this amendment, the Commissioner is authorized to charge our Deposit Account No. 50-0955. A petition for a two-month extension of time is enclosed herewith.

If the Examiner has any further questions, she is respectfully requested to call the undersigned at 212-839-7355.

Respectfully submitted.

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Enc:

I hereby certify that this correspondence is being forwarded via Federal Express, addressed to: U.S. Patent and Trademark Office, 2011 South Clark Place, Customer Window, Crystal Plaza Two, Lobby, Room 1B03, Arlington, VA 22202 on April 15, 2003.

Betty Wright